

## **WRITTEN REQUEST (ISSUED BY THE FDA)**

To obtain needed pediatric information on lorazepam, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below.

To obtain needed pediatric information on lorazepam, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below. These studies investigate the potential uses of lorazepam for ICU sedation and the treatment of status epilepticus.

### **ICU SEDATION**

#### ***Background***

Lorazepam is commonly used for long-term sedation in pediatric and neonatal intensive care units. However, there is limited information available about dosing, pharmacokinetics, effectiveness and safety in pediatric patients who receive sedation with lorazepam in the ICU.

#### ***Type of Study(ies)***

One or more randomized, active control, observer-blinded studies of safety, pharmacokinetic/pharmacodynamic relationship, and dosing in pediatric patients requiring long-term (> 8 hours) sedation in the intensive care unit. The studies will assess safety, effectiveness, and dosing requirements in patients randomized to receive lorazepam by intermittent intravenous bolus, lorazepam by continuous intravenous infusion, or preservative-free midazolam by continuous intravenous infusion, for comparison.

Patients will be followed in the study during the entire course of sedation up to 30 days or more and for at least 3 days following complete discontinuation of treatment. An effort will be made to recruit a broad spectrum of patients who require ICU sedation, including patients with liver failure, renal failure, cardiac failure, concomitant medications, poor prognosis and potential for prolonged (> 7 days) sedation.

#### ***Indication(s) to be Studied (i.e., objective of stud(ies)):***

- a. Assess the effectiveness, safety and dosing requirements for repeated bolus and continuous infusion lorazepam in pediatric ICU patients requiring long-term (>8 hours) continuous sedation.
- b. Monitor for the occurrence of pharmacological withdrawal associated with discontinuation of lorazepam following long-term sedation in the ICU. Assess for risk factors associated with withdrawal, and determine an optimal tapering

- regimen to avoid signs/symptoms of pharmacological withdrawal upon discontinuation of lorazepam for ICU sedation.
- c. Assess the safety of benzyl alcohol and solvents present in the marketed Ativan formulation when used for long-term ICU sedation, or assess the safety of an alternative formulation of lorazepam for long-term ICU sedation.
  - d. Investigate the need for increasing doses of lorazepam with long-term use.
  - e. Assess pharmacokinetics and collect data to explore the relationship between plasma concentrations of lorazepam and clinical measures of sedation and adverse effects for repeat IV bolus and continuous IV infusion of lorazepam, with an attempt to capture special populations (including patients with renal, hepatic, or cardiac dysfunction, concomitant medications, poor prognosis and patients requiring prolonged infusion (> 7 days)).
  - f. Determine optimal dosage range, intervals, and titration schemes for repeated IV bolus and continuous IV infusion of lorazepam.
  - g. Compare the incidence of major morbidity and mortality in patients randomized to intermittent bolus lorazepam versus continuous infusion lorazepam versus continuous infusion preservative-free midazolam.

### ***Age Groups to be Studied***

- a. Term infants < 1 month
- b. 1 month to <3 years
- c. 3 - <13 years
- d. 13 - <18 years

### ***Endpoints to be Studied***

- 1. Safety:
  - a. Withdrawal signs/symptoms
  - b. Adverse events
  - c. Vital signs (HR, BP, RR, pulse oximetry, EKG): limits for defining perturbations in these measurements as adverse events will be pre-defined. Vital signs data will be collected to effectively capture potential hemodynamic and respiratory adverse events associated with initiation of sedation, changes in dose, and administration of bolus doses.
  - d. Urine output
  - e. Laboratory exams (including electrolytes, calcium, lactate, hematology, renal and liver function tests, blood gases). Include specific monitoring for potential toxicities due to preservatives and solvents present in the lorazepam formulation.
  - f. Blood levels of benzyl alcohol (or benzoic acid), propylene glycol, and if feasible, polyethylene glycol will be drawn on a regular schedule and when adverse events potentially caused by these agents occur.

- g. Occurrence of “critical or near-critical” incidents related to inadequate sedation or oversedation
  - h. Severe adverse events (predefined) and mortality
  - i. Fluid volumes administered in delivering lorazepam, midazolam, and all other sedative or analgesic agents
  - j. Incidence of myoclonic seizures
  - k. Total and daily administration of benzyl alcohol, propylene glycol, and polyethylene glycol from lorazepam alone and from all sources combined (if a formulation of lorazepam is used that contains any or all of these inactive ingredients).
2. Pharmacokinetic: Samples will be taken in a subset of neonates in numbers sufficient to characterize PK in neonates. In all other age groups, samples will be taken where feasible. An effort will be made to include patients with renal failure, hepatic failure, or concomitant medications that might affect the pharmacokinetics of lorazepam. Measures of adequacy of sedation will be recorded at the times that blood samples are taken for PK/PD correlation. In addition, as feasible, samples will be taken at time points when dose adjustments are required due to inadequate sedation or oversedation.
3. Pharmacodynamic:
- a. Adequacy of sedation (endpoints must be adequately justified and/or validated and will include assessments by both caretakers and a blinded observer)
  - b. Time to adequate sedation (upon initiation of sedation and after dose adjustments and/or rescue when sedation is judged to be inadequate)
  - c. Time to recovery from sedation (from start of drug tapering/discontinuation)
  - d. Dosing requirements over time, tolerance
  - e. Use of adjunct medications
  - f. Use of rescue doses
  - g. Incidence of inadequate sedation or oversedation (pre-defined with reference to sedation endpoints)
  - h. Adequacy of mechanical ventilation

## **Drug Information**

***Dosage form:*** Approved intravenous formulation or a new formulation without one or more of the inactive ingredients in the currently approved formulation (benzyl alcohol, polyethylene glycol, propylene glycol)

***Route of administration:*** Intravenous

***Regimen:*** bolus and continuous infusion

Bolus dose arm: Patients will be randomized to one of 3 initial bolus doses. Dosing tiers will be prespecified; however, there may be different tiers defined depending upon age group, ventilatory status (mechanical vs. spontaneous ventilation), hemodynamic status, or other clinical factors. The number of different dosing tiers will be kept to a minimum.

Subsequent doses will be given according to criteria defined by the protocol and based on scheduled and unscheduled assessments of adequacy of sedation.

Continuous infusion arms: Initial infusion dosing will be set by protocol, as will be the criteria and manner (increments, time intervals, etc.) by which infusion doses will be increased, decreased, or discontinued. Bolus doses may be used as pre-specified in conjunction with initial dosing, dose increases, need for “rescue,” or for anticipated need in conjunction with temporary increases in stimulation, such as procedures. The dosing regimen will be justified by available pharmacokinetic/pharmacodynamic data, in addition to other available information.

Clinical criteria for rescue dosing, escalation or reduction of dosing will be the same in all arms of the study. Changes in dose or use of rescue doses will be based on the results of regularly scheduled assessments and on unscheduled assessments during the course of patient care as the need arises. Assessments should consider factors including sedation and hemodynamic endpoints. Changes in clinical status, such as changes in severity of illness, or discontinuation of mechanical ventilation with continued need for sedation, can also be the basis for changes in dosing as specified in the protocol. Provision of additional doses in anticipation of a stimulating procedure may be specified in the protocol. Lorazepam or other sedating medications will not be administered to patients except as specified in the protocol.

Patients in each lorazepam arm will be randomized to one of two or more termination regimens when discontinuation of drug is indicated with “rescue” provisions in the event of signs/symptoms of pharmacological withdrawal.

Additional drugs, such as fentanyl, used adjunctively with lorazepam (or the active control) for ICU sedation will be prespecified, and the doses and protocols for changes in doses will also be prespecified. If possible, additional sedative drugs will be limited to one other drug in addition to lorazepam or active control. No benzodiazepines will be administered in addition to lorazepam or midazolam. The criteria for administering additional bolus doses or for changing doses of either lorazepam or the additional sedative drug(s) will be clearly pre-specified, as will be the

criteria for determining which drug to choose when a dose change, additional bolus, or “rescue” dose is indicated by clinical assessment. Neuromuscular blocking agents will be given only when well-defined pre-specified criteria are met, and their use will be avoided altogether when possible.

### ***Drug-Specific Safety Concerns:***

#### **Background**

Propylene glycol (PG) has been associated with adverse effects including seizures, renal toxicity, hyperosmolality, lactic acidosis, hypoglycemia, and hemolysis. The doses that cause toxicity in humans following intravenous exposure have not been well defined; however, there have been several case reports of toxicity at doses close to those likely to be used in conjunction with long term intravenous infusion of Ativan for ICU sedation.

The pharmacokinetics of PG gives additional cause for concern in the pediatric ICU population. Half-life increases markedly in premature infants compared to infants compared to adults (19.3 hours vs. 16.9 hours vs. 2-5 hours, respectively). There is also evidence of nonlinear pharmacokinetics at higher doses. Up to 45% of PG is excreted unchanged by the kidney.

Polyethylene glycol (PEG ) has also been associated with severe toxicities, including high anion gap acidosis, hypercalcemia, hyperosmolality, and renal failure. As for PG, toxic doses of PEG are not well defined in humans after systemic exposure. However, renal failure and death have been reported following intravenous administration of 40 mL/day of PEG 300 (Arch Int Med 1959; 104:710-719).

In neonates, parenteral exposure to benzyl alcohol has been associated with gasping respirations, metabolic acidosis, CNS depression, hypotension, renal failure, seizures, intracranial hemorrhage, hypernatremia, and thrombocytopenia. Doses greater than 99 mg/kg/day have been associated with toxicity. Benzyl alcohol may also exhibit saturable kinetics.

#### **Protocol Design**

The amounts of benzyl alcohol, polyethylene glycol, and propylene glycol administered, from lorazepam and from all other sources, will be projected and tracked. Total daily administration of benzyl alcohol will not approximate or exceed potentially toxic doses (approximately 99 mg/kg/day). Incidents in which administration of drugs, including lorazepam, are limited or curtailed due to toxicity or concerns of reaching potentially toxic levels of benzyl alcohol, polyethylene glycol or propylene glycol will be recorded. If it is projected that potential doses of benzyl alcohol, polyethylene glycol, or propylene glycol from all sources will limit the ability to deliver adequate and efficacious doses of lorazepam, a formulation of lorazepam that is free of the limiting solvent(s) and/or preservative may be developed for these trials.

Appropriate measures must be taken for early identification of potential toxicity due to benzyl alcohol, polyethylene glycol, and propylene glycol, including frequent screening of blood gases, electrolytes, calcium, lactate, hematology, hepatic enzymes, and renal function. In addition, blood levels of benzyl alcohol (or benzoic acid), propylene glycol, and if feasible, polyethylene glycol will be drawn on a regular schedule and also when toxicity from one of these inactive ingredients is suspected. Criteria for discontinuing the test drug due to potential toxicity from these excipients will be pre-specified in the protocol.

The studies will be designed to assess for the development of tolerance (i.e. need for increasing doses over time) with long-term use.

The studies will be designed to assess for signs and symptoms of withdrawal upon discontinuation of lorazepam and to determine an optimal tapering regimen to avoid withdrawal.

***Statistical Information, Including Power of Study and Statistical Assessments:***

The study should be of adequate size to detect a doubling of the rate of serious adverse events or death, assuming a control rate of 18%, with probability 0.8 at significance level 0.05 (two-sided).

Studies will be stratified by age to determine appropriate dosing regimens and to determine lorazepam pharmacokinetics.

At least 10 patients will complete the study in each age group in each arm. At least 5 patients in each age group in each arm will have received  $\geq 48$  hours of continuous sedation.

*Labeling that may result from the studies:* Appropriate sections of the label may be changed to incorporate the findings of the studies.

*Format of reports to be submitted:* Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

